Human Engineered Heart Muscles Engraft and Survive Long-Term in a Rodent Myocardial Infarction Model.

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Public Summary:
Heart failure results from the heart's inability to replace lost muscle due to heart attacks or other diseases. After a heart attack a harmful process termed remodeling results in the heart becoming larger and weaker. One strategy to prevent these effects is via tissue engineering: generating an engineered heart muscle (EHM) patch in vitro from cardiomyocytes made from human embryonic stem cells (ESC-CMs), and then applying it to the injured heart to improve function. Enthusiasm for this approach is tempered by concerns that such EHMs might give rise to tumors or otherwise worsen the heart. We generated EHMs from genetically modified ESC-CMs that expressed the luciferase reporter gene (which allows us to measure cell survival in live animals) and transplanted them onto the hearts of immunodeficient rats with experimentally induced chronic heart failure. We showed that the EHMs survived for at least 3 months and that both patches containing live cells and those made without live cells helped slow down the remodeling process; most importantly, no tumors or other unexpected side effects were observed. The ESC-CMs were observed to become more mature over time in the heart, suggesting that the cardiac environment can cause them to become more like normal adult tissue. These results encourage us to pursue this approach and identify the best mixture of cells to build these EHMs as a potential heart failure treatment.

Scientific Abstract:
RATIONALE: Tissue engineering approaches may improve survival and functional benefits from human embryonic stem cell-derived cardiomyocte (ESC-CM) transplantation, thereby potentially preventing dilative remodelling and progression to heart failure. OBJECTIVE: Assessment of transport stability, long term survival, structural organisation, functional benefits, and teratoma risk of engineered heart muscle (EHM) in a chronic myocardial infarction (MI) model. METHODS AND RESULTS: We constructed EHMs from ESC-CMs and released them for transatlantic shipping following predefined quality control criteria. Two days of shipment did not lead to adverse effects on cell viability or contractile performance of EHMs (n=3, P=0.83, P=0.87). After ischemia / reperfusion (I/R) injury, EHMs were implanted onto immunocompromised rat hearts at 1 month to simulate chronic ischemia. Bioluminescence imaging (BLI) showed stable engraftment with no significant cell loss between week 2 and 12 (n=6, P=0.67), preserving up to 25% of the transplanted cells. Despite high engraftment rates and attenuated disease progression (change in ejection fraction for EHMs -6.7+/-1.4% vs control -10.9+/-1.5%, n>12, P=0.05), we observed no difference between EHMs containing viable or non-viable human cardiomyocytes in this chronic xenotransplantation model (n>12, P=0.41). Grafted cardiomyocytes showed enhanced sarcomere alignment and increased connexin 43 expression at 220 days after transplantation. No teratomas or tumors were found in any of the animals (n=14) used for long-term monitoring. CONCLUSIONS: EHM transplantation led to high engraftment rates, long term survival, and progressive maturation of human cardiomyocytes. However, cell engraftment was not correlated with functional improvements in this chronic MI model. Most importantly, the safety of this approach was demonstrated by the lack of tumor or teratoma formation.